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08/991,628	11/05/1997	JACK L. STOMINGER	HUIP-P02-001	2823
28120	7590	03/17/2004	EXAMINER	
ROPE & GRAY LLP ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624			DIBRINO, MARIANNE NMN	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

08/991,628

**Applicant(s)**

STOMINGER ET AL.

**Examiner**

DiBrino Marianne

**Art Unit**

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on 06 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 3-6, 11 and 13-16 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 3-6, 11 and 13-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

1. Applicant's response filed 11/6/03 is acknowledged and has been entered.

Claims 3-6, 11 and 13-16 are pending and are presently being acted upon.

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. Applicant does not have a reference to parent application serial no. 08/400,796.

The following grounds of rejection remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3-6, 11 and 13-16 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter", *Vas-Cath, Inc. V. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed inventions.

The instant claims encompass a pharmaceutical preparation for tolerization comprising a pharmaceutically acceptable carrier and an isolated human polypeptide effective for tolerizing an individual to an autoantigen, said human polypeptide consisting essentially of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, or consisting essentially of one of SEQ ID

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NOS: 1-7, or of a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein.

The specification does not it provide adequate written description of "human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein", nor consisting essentially of one of SEQ ID NOS: 1-7, nor of a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor does it provide adequate written description of what those MHC core binding residues are and wherein the said polypeptide binds to said HLA-DR protein, and wherein the non-MHC binding residues activates autoreactive T cells from a subject having an autoimmune disease and causes tolerization, nor wherein the HLA-DR protein is associated with a human autoimmune disease. The specification does not disclose what amino acid residues are associated with a *human* polypeptide.

The use for the claimed nucleic acids disclosed in the specification is generation of peptides that bind to an HLA-DR protein associated with an autoimmune disease and which activate autoreactive T cells from a subject having an autoimmune disease and cause tolerization.

The transitional phrase "consisting essentially of" defines the scope of a claim with respect to what unrecited additional components, if any, are excluded from the scope of the claim. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of" for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention."). See also *In re Janakirama-Rao*, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). MPEP 2111.03.

The specification does not define the term "human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein". The specification on page 52 at lines 25-27 discloses that the term "core MHC binding residues" means the residues of an epitope corresponding to the P-1 to P-9 positions of a peptide bound to an HLA-DR molecule. The specification further discloses that there are 5 binding pockets in MHC (class II, DR), P1, P4, P6, P7 and P9 (page 19 at lines 17-25), at least two of which (page 19 at lines 29-31, page 20, lines 5-6) are used via consideration of the chemical nature and size of said binding pockets (page 20 at lines 9-23) for determination of the sequence motif of the corresponding peptide that binds to the MHC molecule (page 19 at lines 29-31).

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Accordingly, the amino acids at a maximum of three of the motif positions may not be motif amino acids and may actually be deleterious to binding. The PV motif #1 of instant claim 5 has only three defined positions, P1, P4 and P6. O'Sullivan (1991) was relied upon in a previous office action mailed 6/16/99 for the teaching that the presence of putative binding motif residues does not necessarily correlate with actual binding to an MHC molecule because both binders and nonbinders may have the putative motif (last sentence in Abstract). In addition, the amino acid residues outside the "core" may also be deleterious to binding. The art recognizes that in order to be used for generating an immunogenic or tolerogenic response that said peptide must bind MHC and also present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding. There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim. With the exception of the specific peptides identified by amino acid sequence in the specification, the skilled artisan cannot envision the detailed structure of the encompassed peptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated peptide is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

In addition, the specification discloses that the peptide may be administered in high doses to produce high dose tolerance, as described in WO 94/06828 page 30 at lines 15-18). The cited WO document, however, teaches substituted tolerizing peptides, i.e., peptides that are generated by replacing each amino acid of the immunogenic peptide with a different amino acid residue and testing for tolerized T cells, i.e., ones that will not proliferate when stimulated with low antigen concentrations.

The specification discloses that HLA-DR4 (DR $\beta$ 1\*0401 and DR $\beta$ 1\*0404) and DR  $\beta$ 1\*0101 are associated with susceptibility to rheumatoid arthritis (paragraph spanning pages 1 and 2), that HLA-DR4 (DR $\beta$ 1\*0402) or a rare HLA-DQ1 (DQ $\beta$ 1\*05032) allele (page 2) are associated with the autoimmune disease pemphigus vulgaris. The specification does not disclose the greater than 70 known HLA-DR allotypes, nor their pocket structures or motifs for peptides that bind to them, and association with susceptibility to autoimmune diseases.

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In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See *The Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In *University of California v. Eli Lilly and Co.*, 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, *id.* at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", *Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd.*, 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606.

Applicant's arguments in the amendment filed 11/6/03 have been fully considered but are not persuasive.

Applicant's position in the said amendment beginning on page 22 and continuing on to page 24 is of record.

It is the Examiner's position that the disclosure of 16 species, i.e., SEQ ID NO: 1-16, which bind to 2 species of HLA class II molecules, i.e., HLA-DR2 or HLA-DR4 and wherein the said peptide/MHC complexes activate autoreactive T cells from a subject having an autoimmune disease, Pemphigus vulgaris for HLA-DR4 and MS for HLA-DR2 is not sufficient relevant identifying characteristics for the instant claims for the reasons of record in the Office Action mailed 7/16/03.

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In addition, there is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim. With the exception of the specific peptides identified by amino acid sequence in the specification, the skilled artisan cannot envision the detailed structure of the encompassed and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated peptide is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

5. Claims 3-6, 11 and 13-16 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3-6, 11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical preparation comprising a human polypeptide consisting of one of SEQ ID NOS: 1-7, does not reasonably provide enablement for the claimed pharmaceutical preparation comprising a human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor consisting essentially of one of SEQ ID NOS: 1-7, nor a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not disclose how to make/and or use a pharmaceutical preparation comprising a human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor *consisting essentially of* one of SEQ ID NOS: 1-7, nor a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass amino acid residues in the P1-P9 "core" that are non-HLA-DR binding amino acid residues at HLA-DR motif binding positions and additionally encompass proteinaceous material which contains sequences outside of the "core" MHC binding residues of a sequence motif for an HLA-DR protein.

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The transitional phrase “consisting essentially of” defines the scope of a claim with respect to what unrecited additional components, if any, are excluded from the scope of the claim. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, “consisting essentially of” will be construed as equivalent to “comprising.” See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 (“PPG could have defined the scope of the phrase consisting essentially of” for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.”). See also *In re Janakirama-Rao*, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). MPEP 2111.03.

The specification does not define the term “human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein.” The specification on page 52 at lines 25-27 discloses that the term “core MHC binding residues” means the residues of an epitope corresponding to the P-1 to P-9 positions of a peptide bound to an HLA-DR molecule. The specification further discloses that there are 5 binding pockets in MHC (class II, DR), P1, P4, P6, P7 and P9 (page 19 at lines 17-25), at least two of which (page 19 at lines 29-31, page 20, lines 5-6) are used via consideration of the chemical nature and size of said binding pockets (page 20 at lines 9-23) for determination of the sequence motif of the corresponding peptide that binds to the MHC molecule (page 19 at lines 29-31).

Accordingly, the amino acids at a maximum of three of the motif positions may not be motif amino acids and may actually be deleterious to binding. The PV motif #1 of instant claim 5 has only three defined positions, P1, P4 and P6. O’Sullivan (1991) was relied upon in a previous office action mailed 6/16/99 for the teaching that the presence of putative binding motif residues does not necessarily correlate with actual binding to an MHC molecule because both binders and nonbinders may have the putative motif (last sentence in Abstract). In addition, the amino acid residues outside the “core” may also be deleterious to binding. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding. There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim.

In addition, the specification discloses that the peptide may be administered in high doses to produce high dose tolerance, as described in WO 94/06828 page 30 at lines 15-18). The cited WO document, however, teaches substituted tolerizing peptides, i.e., peptides that are generated by replacing each amino acid of the immunogenic peptide with a different amino acid residue and testing for tolerized T cells, i.e., ones that will not proliferate when stimulated with low antigen concentrations.



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The specification discloses that HLA-DR4 (DR $\beta$ 1\*0401 and DR $\beta$ 1\*0404) and DR  $\beta$ 1\*0101 are associated with susceptibility to rheumatoid arthritis (paragraph spanning pages 1 and 2), that HLA-DR4 (DR $\beta$ 1\*0402) or a rare HLA-DQ1 (DQ $\beta$ 1\*05032) allele (page 2) are associated with the autoimmune disease pemphigus vulgaris. The specification does not disclose the greater than 70 known HLA-DR allotypes, nor their pocket structures or motifs for peptides that bind to them, and association with susceptibility to human autoimmune diseases.

Evidentiary reference Chicz et al (J. Exp. Med. 1993, 178: 27-47) teaches that *naturally processed* peptides acid-extracted from a variety of HLA-DR alleles ranged from 10-34 amino acid residues in length (especially Abstract). It was known to the skilled artisan at the time the invention was made that Class II MHC/HLA molecules are capable of binding larger exogenous peptides. The instant claims, do not recite a length limitation for the polypeptide. In addition, particularly in longer polypeptides, the amino acid residues outside of the core amino acid residues would render the polypeptide susceptible to other frames of binding to the HLA molecule than the intended frame consisting of the motif amino acid residues.

There is no guidance in the specification as to what alterations result in a functional polypeptide, i.e., one that binds to HLA-DR (except for 3 defined of 5 HLA-DR4 binding positions) and to a TCR and causes tolerization. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions/additions would be acceptable to retain functional activity, i.e., bind to any number of undisclosed HLA-DR molecules, bind to a T cell and cause tolerization, it would require undue experimentation for one of skill in the art to arrive at amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make and/or use the corresponding sequences. The enablement provided by the specification is not commensurate with the scope of the claims.

Applicant's arguments in the amendment filed 11/6/03 have been fully considered but are not persuasive.

Applicant's position in the said amendment beginning on page 9 and continuing on to page 22 is of record.

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It is the Examiner's position that the disclosure in the specification of "peptides including at least the MHC binding and TCR contact residues are contemplated as equivalents" (page 28 at lines 27-30) is not enabling for what Applicant considers to be the basic and novel characteristics of the claimed polypeptides, i.e., the ability to bind an HLA-DR protein and to activate autoreactive T cells from a subject having an autoimmune disease. The instant claims recite "HLA-DR protein" which limitation encompasses hundreds of HLA-DR proteins and the instant claims recite "wherein the said polypeptide bound to said HLA-DR protein activates autoreactive T cells from a subject having said autoimmune disease" encompasses untold number of polypeptides with amino acid residues which may or may not provide adequate T cell receptor contact residues to provide tolerization in any number of undisclosed autoimmune diseases with disclosed or undisclosed associations with a particular HLA-DR molecule.

It is the Examiner's further position that the skilled artisan was aware at the time the invention was made that class II HLA molecules, such as HLA-DR, are capable of binding larger peptides and even small proteins, and that the ends of the peptide can protrude from the class II HLA binding site, and so long polypeptides fall within the scope of claims 3-5, and in addition within the scope of claims 6, 11 and 13-16. It is the Examiner's position that the polypeptides recited in claims 3-6 and 11 as recited can read on polypeptides of length greater than the length of those SEQ ID NO recited instant claim 6 and are not necessarily relatively small peptides. The skilled artisan was aware at the time the invention was made that peptides longer than 15 amino acids bound to class II MHC proteins.

It is the Examiner's position that the disclosure of "An ever increasing number of autoimmune diseases are now being associated with particular alleles of the MHC class II HLA-DR locus. For most of these autoimmune diseases, the self epitope remains unknown. For some, however, the self protein involved in the autoimmune response is suspected. In one aspect of the present invention, a method is provided for identifying the self epitopes involved in autoimmune diseases associated with HLA-DR alleles" (on page 23 of the instant specification at lines 15-20) is not enabling for the breadth of the instant claims for the reasons of record. The specification on page 23 discloses at lines 23-27 and on to page 24 at lines 1-2 "the method may be applied to any of the autoimmune diseases for which an association with a particular HLA-DR allele is known and for which the amino acid residues forming the MHC binding pockets...for that allele are known." The instant specification at the same location discloses that that said method is to compare peptides to the peptides of the invention, however, the peptide motifs disclosed are for 3 out of 5 positions for binding to a particular MHC class II molecule, the possession of which as enunciated in the instant rejection are not necessary predictive of binding and not of which residues at non MHC class II contact positions are those that are responsible for T cell receptor contact and tolerization.

Regarding Applicant's arguments to guidance being provided by the motif recited in claims 5 and 15, the Examiner points to the arguments in the instant rejection supra.

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Regarding Applicant's arguments to identification of amino acid sequences that have functional activity including the ability to bind to HLA-DR proteins and to activate autoreactive T cells may be determined by assays that were well known to the skilled artisan at the time the application was filed, such as the T cell proliferation assay disclosed in Example 1 of the specification, it is the Examiner's position that the skilled artisan was aware that it is unpredictable in whether tolerization can be produced in vivo despite efficient recognition in vitro, and also the teaching enunciated supra is one of substituted tolerizing peptides that will not proliferate.

It is the Examiner's position that Ngo et al are not being cited in the instant rejection and so Applicant's arguments thereto are moot.

It is the Examiner's position that the skilled artisan would have been aware that tolerization with a preparation comprising a protein or peptide can be dependent upon route of administration and dosage and timing of dosing.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 13-16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 13 is indefinite in the recitation of "wherein said preparation is *free* of a polypeptide corresponding to said sequence" because it is not clear what is meant. The instant claim 13 recites a pharmaceutical preparation comprising an amount of an immunogenic preparation effective to immunize against a human pathogen that in its native form *includes* a polypeptide that has a sequence that binds to an HLA-DR protein.

b. Claim 13 is indefinite in the recitation of "includes a polypeptide" because it is not clear whether said polypeptide is a portion of a protein from a pathogenic organism.

Applicant's arguments in the amendment filed 11/6/03 have been fully considered but are not persuasive.

It is Applicant's position in the said amendment beginning on page 25 with regard to "a." is that the phrase in question is amenable to a single interpretation, specifically the preparation is free of autoantigenic peptides, that is, peptides that bind to HLA-DR and activate autoreactive T cells are not present in the preparation.

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It is the Examiner's position that the claim 13 is not amenable to the single said interpretation. Claim 13 recites a "polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein...wherein said preparation is free of a polypeptide corresponding to said sequence" and "wherein said polypeptide bound to said HLA-DR protein activates autoreactive T cells".

It is Applicant's position in the said amendment filed 11/6/03 with regard to "b." that the phrase clearly indicates that the polypeptide is a portion of a protein from a pathogenic pathogen.

It is the Examiner's position that "a human pathogen in its native form" can refer to a pathogen that has not mutated.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 3-6 and 13-16 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 5,874,531. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition comprising the peptides of claim 3 of the '531 patent are encompassed by the instant claims.

Applicant's arguments in the amendment filed 11/6/03 have been fully considered but are not persuasive.

It is Applicant's position in the said amendment on page 26 at item 5, that the instant application is a division of the application that issued as the '531 patent and as such, 35

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USC 121 prohibits the use of the '531 patent as a reference against the instant application.

It is the Examiner's position that the method recited in instant claim 11 was not restricted from the peptide/composition claims in the parent application, as the application that issued as the '531 patent only contained peptide/composition claims, and the said issued claim 3 encompasses the composition comprising the peptides recited in the instant claims.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 3-5 and 13-15 stand rejected under 35 U.S.C. 102(b) as being anticipated by Amagai et al (Cell, Vol. 67, pages 869-877, 1991) for the reasons of record in Paper No. 12 mailed 6/16/99.

Applicant's arguments in the amendment filed 11/6/03 have been fully considered but are not persuasive.

It is Applicant's position on pages 27 and 28 of the said amendment that independent claims 3 and 13 are intended to embrace polypeptides capable of binding autoimmune associated HLA proteins, not a full-length autoantigenic protein as described in Amagai, that Amagai fails to teach or suggest what short peptides make up self epitopes for pemphigus vulgaris, that the protein disclosed by Amagai would materially affect the basic and novel characteristics of the preparation and therefore is excluded from the scope of claim 3, that one of ordinary skill in the art would recognize that a preparation for tolerization consisting essentially of an isolated peptide is superior to a preparation containing a full-length protein. It is Applicant's further position that claim 13 recites that the preparation is free of a polypeptide corresponding to the said sequence amino acid sequence corresponding to a sequence motif for an HLA-DR protein, that Amagai fails to teach which portions of the protein contain the autoantigen for pemphigus vulgaris.

It is the Examiner's position that claims 3 and 13 encompass the full length protein, that the full length protein has an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, regardless of whether or not those motif residues or the autoantigenic epitope are taught by Amagai et al. It is the Examiner's further position regarding the recitation in claim 13 of "wherein said preparation is free of a polypeptide corresponding to said sequence", that the claim also recites "a polypeptide having an amino acid sequence motif for an HLA-DR

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protein...wherein said preparation is free of a polypeptide corresponding to said sequence" and "wherein said polypeptide bound to said HLA-DR protein activates autoreactive T cells". It is the Examiner's position that one of ordinary skill in the art at the time the invention was made would have been aware that tolerization with a preparation comprising a protein or peptide can be dependent upon route of administration and dosage and timing of dosing.

12. No claim is allowed.

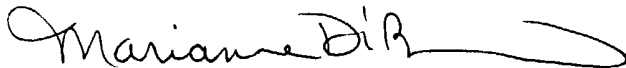
13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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